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=> s MPEP
L1            1 MPEP

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   96206-92-7  REGISTRY
ED   Entered STN:  04 May 1985
CN   Pyridine, 2-methyl-6-(2-phenylethynyl)-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   2-Picoline, 6-phenylethynyl- (6CI)
CN   Pyridine, 2-methyl-6-(phenylethynyl)- (9CI)
OTHER NAMES:
CN   2-Methyl-6-(phenylethynyl)pyridine
CN   MPEP
MF   C14 H11 N
CI   COM
LC   STN Files:   AGRICOLA, BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT,
       CHEMCATS, CIN, CSCHEM, IMSDRUGNEWS, IMSRESEARCH, TOXCENTER, USPAT2,
       USPATFULL
         (*File contains numerically searchable property data)
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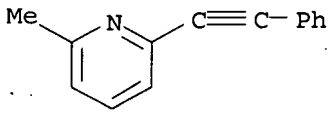

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

188 REFERENCES IN FILE CA (1907 TO DATE)
188 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> file medicine
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

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FULL ESTIMATED COST	7.80	8.01

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=> s l1
L2 1461 L1

=> s gastroesophageal reflux

```
L3        96118 GASTROESOPHAGEAL REFLUX

=> s GERD
L4        27323 GERD

=> s transient lower esophageal shincter relaxations
  27 FILES SEARCHED...
L5            0 TRANSIENT LOWER ESOPHAGEAL SHINCTER RELAXATIONS

=> s transient lower esophageal sphincter
L6         1276 TRANSIENT LOWER ESOPHAGEAL SPHINCTER

=> s lower esophageal sphincter
L7        19358 LOWER ESOPHAGEAL SPHINCTER

=> s regurgitation
L8        91830 REGURGITATION

=> s l3 or l4 or l6 or l7 or l8
  27 FILES SEARCHED...
L9       201001 L3 OR L4 OR L6 OR L7 OR L8

=> s l2 and l9
L10           17 L2 AND L9

=> d l10 1-17 bib abs kwic

L10  ANSWER 1 OF 17  BIOSIS  COPYRIGHT (c) 2007 The Thomson Corporation  on STN
AN   2007:204347  BIOSIS
DN   PREV200700195616
TI   Peripheral versus central modulation of gastric vagal pathways by
     metabotropic glutamate receptor 5.
AU   Young, Richard L. [Reprint Author]; Page, Amanda J.; O'Donnell, Tracey A.;
     Cooper, Nicole J.; Blackshaw, L. Ashley
CS   Level 1 Hanson Inst, Nerve Gut Res Lab, Frome Rd, Adelaide, SA 5000,
     Australia
     richard.young@adelaide.edu.au
SO   American Journal of Physiology - Gastrointestinal and Liver Physiology,
     (FEB 2007) Vol. 292, No. 2, pp. G501-G511.
     ISSN: 0193-1857.
DT   Article
LA   English
ED   Entered STN: 21 Mar 2007
     Last Updated on STN: 21 Mar 2007
AB   Metabotropic glutamate receptors (mGluR) are classified into group I, II,
     and III mGluR.  Group I (mGluR1, mGluR5) are excitatory, whereas group II
     and III are inhibitory. mGluR5 antagonism potently reduces triggering of
     transient lower esophageal sphincter
     relaxations and gastroesophageal reflux.
     Transient lower esophageal sphincter
     relaxations are mediated via a vagal pathway and initiated by distension
     of the proximal stomach.  Here, we determined the site of action of mGluR5
     in gastric vagal pathways by investigating peripheral responses of ferret
     gastroesophageal vagal afferents to graded mechanical stimuli in vitro and
     central responses of nucleus tractus solitarius (NTS) neurons with gastric
     input in vivo in the presence or absence of the mGluR5 antagonist
     2-methyl-6-(phenylethynyl) pyridine (MPEP). mGluR5 were also identified
     immunohistochemically in the nodose ganglia and NTS after extrinsic vagal
     inputs had been traced from the proximal stomach.  Gastroesophageal vagal
     afferents were classified as mucosal, tension, or tension-mucosal (TM)
     receptors.  MPEP (1-10 mu M) inhibited responses to circumferential
     tension of tension and TM receptors.  Responses to mucosal stroking of
     mucosal and TM receptors were unaffected.  MPEP (0.001-10 nmol icv) had no
     major effect on the majority of NTS neurons excited by gastric distension
```

or on NTS neurons inhibited by distension. mGluR5 labeling was abundant in gastric vagal afferent neurons and sparse in fibers within NTS vagal subnuclei. We conclude that mGluR5 play a prominent role at gastroesophageal vagal afferent endings but a minor role in central gastric vagal pathways. Peripheral mGluR5 may prove a suitable target for reducing mechanosensory input from the periphery, for therapeutic benefit.

AB. . . mGluR. Group I (mGluR1, mGluR5) are excitatory, whereas group II and III are inhibitory. mGluR5 antagonism potently reduces triggering of transient lower esophageal sphincter relaxations and gastroesophageal reflux. Transient lower esophageal sphincter relaxations are mediated via a vagal pathway and initiated by distension of the proximal stomach. Here, we determined the site. . .

IT . . .

IT Parts, Structures, & Systems of Organisms
stomach: digestive system; esophagus: digestive system; nucleus tractus solitarius: nervous system

IT Diseases
gastroesophageal reflux: digestive system disease
Gastroesophageal Reflux (MeSH)

IT Chemicals & Biochemicals
2-methyl-6-(phenylethynyl)pyridine; metabotropic glutamate receptor 5 [mGluR5]; metabotropic glutamate receptor 1 [mGluR1]

RN 96206-92-7 (2-methyl-6-(phenylethynyl)pyridine)

L10 ANSWER 2 OF 17 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

AN 2006:79438 BIOSIS

DN PREV200600086179

TI The metabotropic glutamate receptor 5 antagonist MPEP inhibits transient lower esophageal sphincter relaxations in the dog.

AU Jensen, Jorgen; Lehmann, Anders; Hulander, Malin; Uvebrant, Anna; Carlsson, Anita; Umaerus, Mia; Nilsson, Karolina; Frisby, Claudine; Blackshaw, L. Ashley; Mattsson, Jan

SO Gastroenterology, (APR 2004) Vol. 126, No. 4, Suppl. 2, pp. A632. Meeting Info.: Digestive Disease Week/105th Annual Meeting of the American-Gastroenterological-Association. New Orleans, LA, USA. May 16 -20, 2004. Amer Gastroenterol Assoc.
CODEN: GASTAB. ISSN: 0016-5085.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 25 Jan 2006
Last Updated on STN: 25 Jan 2006

AB Transient lower esophageal sphincter relaxations (TLESRs) are the major cause of gastroesophageal acid reflux and are initiated by stimulation of gastric vagal afferents following postprandial gastric distension. The metabotropic glutamate receptors (mGluR) belong to family III of G-protein coupled receptors. Eight different mGluRs (mGluR1-mGluR8) have been identified and these can, based on sequence homology, signal transduction mechanisms and pharmacology, be divided into three groups (I-III). The aim of the present study was to investigate the effect of the selective mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) on TLESRs in the dog. Labrador retrievers equipped with esophagostomies were intubated with a multilumen Dentsleeve assembly and a pH electrode. Pressures were recorded from the stomach, lower esophageal sphincter (LES) and esophagus, as well as from the pharynx. In order to assess the affinity of MPEP for the canine mGluR5, saturation binding analysis of tritiated MPEP to dog brain membranes was performed. The expression of mGluR5 in nodose ganglion, containing the cell bodies of gastric vagal afferents, was investigated using RT-PCR. MPEP (1.4-8.7 mu mol/kg; n = 3-4) produced a dose-dependent reduction of TLESRs. The maximum inhibition obtained with the highest dose was 59 +/- 11%. No significant

effects were seen on basal LES pressure, swallowing or on esophageal peristalsis. The binding affinity of MPEP at dog mGluR5 was 16 4.6 nM, i.e. similar to the affinity for the human mGluR5. RT-PCR analysis showed expression of mGluR5 mRNA in dog nodose ganglion. It is concluded that the mGluR5 antagonist MPEP has an inhibitory effect on TLESRs and that gastric vagal afferents may be one site of action for this effect. These results suggest that mGluR5 is a potential target for the treatment of gastroesophageal reflux disease.

TI The metabotropic glutamate receptor 5 antagonist MPEP inhibits transient lower esophageal sphincter relaxations in the dog.

AB Transient lower esophageal sphincter relaxations (TLESRs) are the major cause of gastroesophageal acid reflux and are initiated by stimulation of gastric vagal afferents following. . . equipped with esophagostomies were intubated with a multilumen Dentsleeve assembly and a pH electrode. Pressures were recorded from the stomach, lower esophageal sphincter (LES) and esophagus, as well as from the pharynx. In order to assess the affinity of MPEP for the canine. . . one site of action for this effect. These results suggest that mGluR5 is a potential target for the treatment of gastroesophageal reflux disease.

IT . . .

& Systems of Organisms
esophagus: digestive system; nodose ganglion: nervous system; pharynx: dental and oral system; brain membrane: nervous system; lower esophageal sphincter: digestive system, muscular system; gastric vagal afferent: digestive system, nervous system

IT Diseases
gastroesophageal reflux disease: digestive system
disease, drug therapy
Gastroesophageal Reflux (MeSH)

IT Chemicals & Biochemicals
mRNA [messenger RNA]: expression; metabotropic glutamate receptor 5 [mGluR 5]: expression, regulation; 2-methyl-6-(phenylethynyl)-pyridine [MPEP]: gastrointestinal-drug, . . .

IT Methods & Equipment
esophagostomy: laboratory techniques, experimental surgical techniques

IT Miscellaneous Descriptors
lower esophageal sphincter pressure; lower esophageal sphincter relaxation

RN 96206-92-7 (2-methyl-6-(phenylethynyl)-pyridine)
96206-92-7 (MPEP)

L10 ANSWER 3 OF 17 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

AN 2005:540997 BIOSIS

DN PREV200510318147

TI Transient lower esophageal sphincter relaxations in dogs are inhibited by a metabotropic glutamate receptor 5 antagonist.

AU Jensen, Jorgen [Reprint Author]; Lehmann, Anders; Uvebrant, Anna; Carlsson, Anita; Jerndal, Gunilla; Nilsson, Karolina; Frisby, Claudine; Blackshaw, L. Ashley; Mattsson, Jan P.

CS AstraZeneca R and D Molndal, Integrat Pharmacol, Gastrointestinal Biol, S-43183 Molndal, Sweden
jorgen.m.jensen@astrazeneca.com

SO European Journal of Pharmacology, (SEP 5 2005) Vol. 519, No. 1-2, pp. 154-157.
CODEN: EJPHAZ. ISSN: 0014-2999.

DT Article

LA English

ED Entered STN: 1 Dec 2005
Last Updated on STN: 1 Dec 2005

AB Transient lower esophageal sphincter relaxation is the major mechanism for gastroesophageal

reflux. The present study was initiated to investigate the potential effect of the metabotropic glutamate 5 (mGlu5) receptor antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), on transient lower esophageal sphincter relaxations in the conscious dog. MPEP (1.4-8.7 mu mol/kg i.v.) produced a dose-dependent inhibition of transient lower esophageal sphincter relaxations (59 +/- 11 % inhibition at 8.7 mu mol/kg). In addition, there was a reduction of the number of reflux. episodes and an increase in latency time to the occurrence of the first transient lower esophageal sphincter relaxation. No effect was seen on basal lower esophageal sphincter pressure or on swallowing.It is concluded that the mGlu5 receptor antagonist MPEP potently inhibits transient lower esophageal sphincter relaxations and that the mGlu5 receptor is a potential target for treatment of gastroesophageal reflux disease. (c) 2005 Elsevier B.V. All rights reserved.

TI Transient lower esophageal sphincter relaxations in dogs are inhibited by a metabotropic glutamate receptor 5 antagonist.

AB Transient lower esophageal sphincter relaxation is the major mechanism for gastroesophageal reflux. The present study was initiated to investigate the potential effect of the metabotropic glutamate 5 (mGlu5) receptor antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), on transient lower esophageal sphincter relaxations in the conscious dog. MPEP (1.4-8.7 mu mol/kg i.v.) produced a dose-dependent inhibition of transient lower esophageal sphincter relaxations (59 +/- 11 % inhibition at 8.7 mu mol/kg). In addition, there was a reduction of the number of reflux. episodes and an increase in latency time to the occurrence of the first transient lower esophageal sphincter relaxation. No effect was seen on basal lower esophageal sphincter pressure or on swallowing.It is concluded that the mGlu5 receptor antagonist MPEP potently inhibits transient lower esophageal sphincter relaxations and that the mGlu5 receptor is a potential target for treatment of gastroesophageal reflux disease. (c) 2005 Elsevier B.V. All rights reserved.

IT . . .
Muscular System (Movement and Support)

IT Parts, Structures, & Systems of Organisms
esophageal sphincter: digestive system, muscular system

IT Diseases
gastroesophageal reflux: digestive system disease
Gastroesophageal Reflux (MeSH)

IT Chemicals & Biochemicals
metabotropic glutamate receptor: antagonism; 2-methyl-6-(phenylethynyl)-pyridine: gastrointestinal-drug, gastric secretion inhibitor-drug

RN 96206-92-7 (2-methyl-6-(phenylethynyl)-pyridine)

L10 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1091076 CAPLUS
DN 144:121431
TI Inhibition of transient lower esophageal sphincter relaxation and gastroesophageal reflux by metabotropic glutamate receptor ligands
AU Frisby, Claudine L.; Mattsson, Jan P.; Jensen, Joergen M.; Lehmann, Anders; Dent, John; Blackshaw, L. Ashley
CS Nerve-Gut Research Laboratory, Royal Adelaide Hospital, Adelaide, Australia
SO Gastroenterology (2005), 129(3), 995-1004
CODEN: GASTAB; ISSN: 0016-5085
PB Elsevier Inc.

DT Journal
LA English
AB Background & Aims: Transient lower esophageal sphincter relaxation (TLESR) is the major mechanism of gastroesophageal acid reflux. TLESR is mediated via vagal pathways, which may be modulated by metabotropic glutamate receptors (mGluRs). Group I mGluRs (mGluR1 and 5) have excitatory effects on neurons, whereas group II (mGluR2 and 3) and group III (mGluR4, 6, 7, and 8) are inhibitory. This study determined the effect of mGluRs on triggering of TLESR and reflux in an established conscious ferret model. Methods: Esophageal manometric/pH studies were performed in ferrets with chronic esophagostomies. TLESR were induced by a gastric load of 25 mL glucose (pH 3.5) and 30 mL air. Results: In control treated animals, gastric load induced 3.52 ± 0.46 TLESRs per 47-min study, 89.7% of which were associated with reflux episodes (n = 16). The mGluR5 antagonist MPEP inhibited TLESR dose dependently, with maximal 71% ± 7% inhibition at 35 μmol/kg (n = 9; P < .0001). MPEP also significantly reduced reflux episodes (P < .001) and increased basal lower esophageal sphincter pressure (P < .05). MPEP inhibited swallowing dose dependently, suggesting a common action on trigger mechanisms for swallowing and TLESR. The more selective analog, MTEP, had more potent effects (90% ± 6% inhibition TLESR at 40 μmol/kg; n = 8; P < .0001). In contrast, the group I agonist DHPG tended to increase TLESR. The group II agonist (2R, 4R)-APDC was ineffective, whereas the group III agonist L-AP4 slightly reduced TLESR (33% at 11 μmol/kg; P < .05). The selective mGluR5 agonist (S)-3, 4-DCPG inhibited TLESR by 54% at 15 μmol/kg (P < .01). Conclusions: mGluR5 antagonists potently inhibit TLESR and reflux in ferrets, implicating mGluR5 in the mechanism of TLESR. MGluR5 antagonists are therefore promising as therapy for patients with GERD.
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Inhibition of transient lower esophageal sphincter relaxation and gastroesophageal reflux by metabotropic glutamate receptor ligands
AB Background & Aims: Transient lower esophageal sphincter relaxation (TLESR) is the major mechanism of gastroesophageal acid reflux. TLESR is mediated via vagal pathways, which may be modulated by metabotropic glutamate receptors (mGluRs). Group I mGluRs (mGluR1 and 5) have excitatory effects on neurons, whereas group II (mGluR2 and 3) and group III (mGluR4, 6, 7, and 8) are inhibitory. This study determined the effect of mGluRs on triggering of TLESR and reflux in an established conscious ferret model. Methods: Esophageal manometric/pH studies were performed in ferrets with chronic esophagostomies. TLESR were induced by a gastric load of 25 mL glucose (pH 3.5) and 30 mL air. Results: In control treated animals, gastric load induced 3.52 ± 0.46 TLESRs per 47-min study, 89.7% of which were associated with reflux episodes (n = 16). The mGluR5 antagonist MPEP inhibited TLESR dose dependently, with maximal 71% ± 7% inhibition at 35 μmol/kg (n = 9; P < .0001). MPEP also significantly reduced reflux episodes (P < .001) and increased basal lower esophageal sphincter pressure (P < .05). MPEP inhibited swallowing dose dependently, suggesting a common action on trigger mechanisms for swallowing and TLESR. The more selective analog, MTEP, had more potent effects (90% ± 6% inhibition TLESR at 40 μmol/kg; n = 8; P < .0001). In contrast, the group I agonist DHPG tended to increase TLESR. The group II agonist (2R, 4R)-APDC was ineffective, whereas the group III agonist L-AP4 slightly reduced TLESR (33% at 11 μmol/kg; P < .05). The selective mGluR5 agonist (S)-3, 4-DCPG inhibited TLESR by 54% at 15 μmol/kg (P < .01). Conclusions: mGluR5 antagonists potently inhibit TLESR and reflux in ferrets, implicating mGluR5 in the mechanism of TLESR. MGluR5 antagonists are therefore promising as therapy for patients with GERD.
ST esophageal sphincter relaxation metabotropic glutamate receptor gastroesophageal reflux disease
IT Digestive tract, disease

(gastroesophageal reflux; metabotropic glutamate receptor inhibitor 2-methyl-6-(phenylethynyl)-pyridine reduced gastroesophageal reflux episode in ferret model for chronic esophagostomies)

IT Glutamate agonists
(metabotropic glutamate receptor agonist DHPG but not (2R, 4R)-APDC, L-(AP4 and (S)-3, 4-DCPG increased transient lower esophageal sphincter relaxation in ferret model for chronic esophagostomies)

IT Drug targets
Gastrointestinal agents
(metabotropic glutamate receptor inhibitor 2-methyl-6-(phenylethynyl)-pyridine inhibited TLESR and swallowing, reduced reflux episode and increased basal lower esophageal sphincter pressure in ferret model for chronic esophagostomies)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic; metabotropic glutamate receptor inhibitor 2-methyl-6-(phenylethynyl)-pyridine inhibited TLESR and swallowing, reduced reflux episode and increased basal lower esophageal sphincter pressure in ferret model for chronic esophagostomies)

IT Esophagus
(sphincter, gastroesophageal; metabotropic glutamate receptor inhibitor 2-methyl-6-(phenylethynyl)-pyridine potently inhibited transient lower esophageal sphincter relaxation in ferret model for chronic esophagostomies)

IT 146255-66-5, 3,5-Dihydroxyphenylglycine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(group I metabotropic glutamate receptor agonist (R,S)-3, 5-dihydroxyphenylglycine increased transient lower esophageal sphincter relaxation in ferret model for chronic esophagostomies)

IT 169209-63-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(group II metabotropic glutamate receptor agonist (2R,4R)-4-aminopyrrolidine-2, 4-dicarboxylate was ineffective in reducing transient lower esophageal sphincter relaxation in ferret model for chronic esophagostomies)

IT 23052-81-5, L-(+)-2-Amino-4-phosphonobutyric acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(group III metabotropic glutamate receptor agonist L-AP4 slightly reduced transient lower esophageal sphincter relaxation in ferret model for chronic esophagostomies)

IT 176796-64-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metabotropic glutamate receptor agonist (S)-3, 4-dicarboxyphenylglycine inhibited transient lower esophageal sphincter relaxation in ferret model for chronic esophagostomies)

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metabotropic glutamate receptor inhibitor 2-methyl-6-(phenylethynyl)-pyridine inhibited TLESR and swallowing, reduced reflux episode and increased basal lower esophageal sphincter pressure in ferret model for chronic esophagostomies)

IT 329205-68-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metabotropic glutamate receptor inhibitor 3-([2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine inhibited TLESR and swallowing, reduced reflux episode and increased basal lower esophageal sphincter pressure in ferret with chronic esophagostomies)

L10 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:978510 CAPLUS
DN 143:260011
TI Transient lower esophageal sphincter relaxations in dogs are inhibited by a metabotropic glutamate receptor 5 antagonist
AU Jensen, Joergen; Lehmann, Anders; Uvebrant, Anna; Carlsson, Anita; Jerndal, Gunilla; Nilsson, Karolina; Frisby, Claudine; Blackshaw, L. Ashley; Mattsson, Jan P.
CS AstraZeneca R&D Moelndal, Moelndal, S-431 83, Swed.
SO European Journal of Pharmacology (2005), 519(1-2), 154-157
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier B.V.
DT Journal
LA English
AB Transient lower esophageal sphincter relaxation is the major mechanism for gastroesophageal reflux. The present study was initiated to investigate the potential effect of the metabotropic glutamate 5 (mGlu5) receptor antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), on transient lower esophageal sphincter relaxations in the conscious dog. MPEP (1.4-8.7 μmol/kg i.v.) produced a dose-dependent inhibition of transient lower esophageal sphincter relaxations (59±11% inhibition at 8.7 μmol/kg). In addition, there was a reduction of the number of reflux episodes and an increase in latency time to the occurrence of the first transient lower esophageal sphincter relaxation. No effect was seen on basal lower esophageal sphincter pressure or on swallowing. It is concluded that the mGlu5 receptor antagonist MPEP potently inhibits transient lower esophageal sphincter relaxations and that the mGlu5 receptor is a potential target for treatment of gastroesophageal reflux disease.
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Transient lower esophageal sphincter relaxations in dogs are inhibited by a metabotropic glutamate receptor 5 antagonist
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ST mGluR5 antagonist esophageal sphincter relaxation gastroesophageal reflux

IT Digestive tract, disease
(gastroesophageal reflux; transient lower esophageal sphincter relaxations in dogs are inhibited by metabotropic glutamate receptor 5 antagonist)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR5; transient lower esophageal sphincter relaxations in dogs are inhibited by metabotropic glutamate receptor 5 antagonist)

IT Esophagus
(sphincter, gastroesophageal; transient lower esophageal sphincter relaxations in dogs are inhibited by metabotropic glutamate receptor 5 antagonist)

IT Drug targets
Gastrointestinal agents
Glutamate agonists
(transient lower esophageal sphincter relaxations in dogs are inhibited by metabotropic glutamate receptor 5 antagonist)

IT 96206-92-7, MPEP
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(transient lower esophageal sphincter relaxations in dogs are inhibited by metabotropic glutamate receptor 5 antagonist)

L10 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:2699 CAPLUS
DN 140:53471
TI Use of metabotropic glutamate receptor 5 (MGLUR5) antagonists for the treatment of gastroesophageal reflux disease (GERD) and other conditions
IN Lehmann, Anders; Mattsson, Jan
PA Astrazeneca AB, Swed.; NPS Pharmaceuticals, Inc.
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004000316	A1	20031231	WO 2003-US16223	20030619
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2489730	A1	20031231	CA 2003-2489730	20030619
	AU 2003241585	A1	20040106	AU 2003-241585	20030619
	BR 2003011759	A	20050308	BR 2003-11759	20030619
	EP 1513525	A1	20050316	EP 2003-731333	20030619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	CN 1662235	A	20050831	CN 2003-814176	20030619
	JP 2006507225	T	20060302	JP 2004-515703	20030619
	NO 2005000154	A	20050111	NO 2005-154	20050111
	US 2006128760	A1	20060615	US 2005-517869	20051012

PRAI SE 2002-1943 A 20020620
WO 2003-US16223 W 20030619

AB The invention discloses the use of metabotropic glutamate receptor 5 antagonists for the inhibition of transient lower esophageal sphincter relaxations. The invention also discloses the use of metabotropic glutamate receptor 5 antagonists for the treatment of gastroesophageal reflux disease, as well as for the treatment of regurgitation, asthma, chronic laryngitis, lung disease, and failure to thrive.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Use of metabotropic glutamate receptor 5 (MGLUR5) antagonists for the treatment of gastroesophageal reflux disease (GERD) and other conditions

AB The invention discloses the use of metabotropic glutamate receptor 5 antagonists for the inhibition of transient lower esophageal sphincter relaxations. The invention also discloses the use of metabotropic glutamate receptor 5 antagonists for the treatment of gastroesophageal reflux disease, as well as for the treatment of regurgitation, asthma, chronic laryngitis, lung disease, and failure to thrive.

ST metabotropic glutamate receptor 5 antagonist treatment gastroesophageal reflux disease; transient lower esophageal sphincter relaxation MGLUR5 antagonist; regurgitation asthma chronic laryngitis MGLUR5 antagonist; lung disease failure to thrive MGLUR5 antagonist

IT Larynx, disease
(chronic laryngitis; metabotropic glutamate receptor 5 antagonists for treatment of gastroesophageal reflux disease and other conditions)

IT Disease, animal
(failure to thrive; metabotropic glutamate receptor 5 antagonists for treatment of gastroesophageal reflux disease and other conditions)

IT Digestive tract, disease
(gastroesophageal reflux; metabotropic glutamate receptor 5 antagonists for treatment of gastroesophageal reflux disease and other conditions)

IT Antiasthmatics
Asthma
Gastrointestinal agents
Lung, disease
(metabotropic glutamate receptor 5 antagonists for treatment of gastroesophageal reflux disease and other conditions)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR5; metabotropic glutamate receptor 5 antagonists for treatment of gastroesophageal reflux disease and other conditions)

IT Disease, animal
(regurgitation; metabotropic glutamate receptor 5 antagonists for treatment of gastroesophageal reflux disease and other conditions)

IT Esophagus
(sphincter, gastroesophageal, transient lower esophageal sphincter relaxation; metabotropic glutamate receptor 5 antagonists for treatment of gastroesophageal reflux disease and other conditions)

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine 219911-35-0
327056-26-8 453567-01-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metabotropic glutamate receptor 5 antagonists for treatment of gastroesophageal reflux disease and other conditions)

L10 ANSWER 7 OF 17 Elsevier BIOBASE COPYRIGHT 2007 Elsevier Science B.V. on STN

AN 2007054266 ESBIOBASE

TI Peripheral versus central modulation of gastric vagal pathways by metabotropic glutamate receptor 5

AU Young R.L.; Page A.J.; O'Donnell T.A.; Cooper N.J.; Blackshaw L.A.

CS R.L. Young, Nerve-Gut Research Laboratory, Hanson Institute, Frome Rd., Adelaide, SA 5000, Australia.
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SO American Journal of Physiology - Gastrointestinal and Liver Physiology, (2007), 292/2 (G501-G511), 48 reference(s)
CODEN: APGPDF ISSN: 0193-1857 E-ISSN: 1522-1547

DT Journal; Article

CY United States

LA English

SL English

AB Metabotropic glutamate receptors (mGluR) are classified into group I, II, and III mGluR. Group I (mGluR1, mGluR5) are excitatory, whereas group II and III are inhibitory. mGluR5 antagonism potently reduces triggering of transient lower esophageal sphincter
relaxations and gastroesophageal reflux.
Transient lower esophageal sphincter
relaxations are mediated via a vagal pathway and initiated by distension of the proximal stomach. Here, we determined the site of action of mGluR5 in gastric vagal pathways by investigating peripheral responses of ferret gastro-esophageal vagal afferents to graded mechanical stimuli in vitro and central responses of nucleus tractus solitarius (NTS) neurons with gastric input in vivo in the presence or absence of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP). mGluR5 were also identified immunohistochemically in the nodose ganglia and NTS after extrinsic vagal inputs had been traced from the proximal stomach. Gastroesophageal vagal afferents were classified as mucosal, tension, or tension-mucosal (TM) receptors. MPEP (1-10 μM) inhibited
responses to circumferential tension of tension and TM receptors. Responses to mucosal stroking of mucosal and TM receptors were unaffected. MPEP (0.001-10 nmol icv) had no major effect on the majority of NTS neurons excited by gastric distension or on NTS neurons inhibited by distension. mGluR5 labeling was abundant in gastric vagal afferent neurons and sparse in fibers within NTS vagal subnuclei. We conclude that mGluR5 play a prominent role at gastroesophageal vagal afferent endings but a minor role in central gastric vagal pathways. Peripheral mGluR5 may prove a suitable target for reducing mechanosensory input from the periphery, for therapeutic benefit. Copyright .COPYRGT. 2007 the American Physiological Society.

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Transient lower esophageal sphincter
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L10 ANSWER 8 OF 17 Elsevier BIOBASE COPYRIGHT 2007 Elsevier Science B.V. on STN

AN 2006033613 ESBIOBASE

TI Transient lower esophageal sphincter relaxations in dogs are inhibited by a metabotropic glutamate receptor 5 antagonist

AU Jensen J.; Lehmann A.; Uvebrant A.; Carlsson A.; Jerndal G.; Nilsson K.; Frisby C.; Blackshaw L.A.; Mattsson J.P.

CS J. Jensen, Integrative Pharmacology, Gastrointestinal Biology, AstraZeneca R and D Molndal, S-431 83 Molndal, Sweden.
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SO European Journal of Pharmacology, (05 SEP 2005), 519/1-2 (154-157), 21 reference(s)
CODEN: EJPHAZ ISSN: 0014-2999

PUI S0014299905007375

DT Journal; Article

CY Netherlands

LA English

SL English

AB Transient lower esophageal sphincter relaxation is the major mechanism for gastroesophageal reflux. The present study was initiated to investigate the potential effect of the metabotropic glutamate 5 (mGlu5) receptor antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), on transient lower esophageal sphincter relaxations in the conscious dog. MPEP (1.4-8.7 μmol/kg i.v.) produced a dose-dependent inhibition of transient lower esophageal sphincter relaxations (59 ± 11% inhibition at 8.7 μmol/kg). In addition, there was a reduction of the number of reflux episodes and an increase in latency time to the occurrence of the first transient lower esophageal sphincter relaxation. No effect was seen on basal lower esophageal sphincter pressure or on swallowing. It is concluded that the mGlu5 receptor antagonist MPEP potently inhibits transient lower esophageal sphincter relaxations and that the mGlu5 receptor is a potential target for treatment of gastroesophageal reflux disease. .COPYRGT. 2005 Elsevier B.V. All rights reserved.

TI Transient lower esophageal sphincter relaxations in dogs are inhibited by a metabotropic glutamate receptor 5 antagonist

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ST Glutamate; Lower esophageal sphincter; 2-methyl-6-(phenylethynyl)-pyridine; MPEP;

Gastroesophageal reflux

L10 ANSWER 9 OF 17 Elsevier BIOBASE COPYRIGHT 2007 Elsevier Science B.V. on STN
AN 2005233329 ESBIOBASE
TI Inhibition of transient lower esophageal sphincter relaxation and gastroesophageal reflux by metabotropic glutamate receptor ligands
AU Frisby C.L.; Mattsson J.P.; Jensen J.M.; Lehmann A.; Dent J.; Blackshaw L.A.
CS Dr. L.A. Blackshaw, Nerve Gut Research Laboratory, Hanson Institute, Frome Road, Adelaide, SA 5000, Australia.
E-mail: ablacksh@mail.rah.sa.gov.au
SO Gastroenterology, (2005), 129/3 (995-1004), 45 reference(s)
CODEN: GASTAB ISSN: 0016-5085
PUI S0016508505013570
DT Journal; Article
CY United States
LA English
SL English
AB Background & Aims: Transient lower esophageal sphincter relaxation (TLESR) is the major mechanism of gastroesophageal acid reflux. TLESR is mediated via vagal pathways, which may be modulated by metabotropic glutamate receptors (mGluRs). Group I mGluRs (mGluR1 and 5) have excitatory effects on neurons, whereas group II (mGluR2 and 3) and group III (mGluR4, 6, 7, and 8) are inhibitory. This study determined the effect of mGluRs on triggering of TLESR and reflux in an established conscious ferret model. Methods: Esophageal manometric/pH studies were performed in ferrets with chronic esophagostomies. TLESR were induced by a gastric load of 25 mL glucose (pH 3.5) and 30 mL air. Results: In control treated animals, gastric load induced 3.52 ± 0.46 TLESRs per 47-minute study, 89.7% of which were associated with reflux episodes (n = 16). The mGluR5 antagonist MPEP inhibited TLESR dose dependently, with maximal 71% ± 7% inhibition at 35 μmol/kg (n = 9; P < .0001). MPEP also significantly reduced reflux episodes (P < .001) and increased basal lower esophageal sphincter pressure (P < .05). MPEP inhibited swallowing dose dependently, suggesting a common action on trigger mechanisms for swallowing and TLESR. The more selective analogue, MTEP, had more potent effects (90% ± 6% inhibition TLESR at 40 μmol/kg; n = 8; P < .0001). In contrast, the group I agonist DHPG tended to increase TLESR. The group II agonist (2R, 4R)-APDC was ineffective, whereas the group III agonist L-(AP4 slightly reduced TLESR (33% at 11 μmol/kg; P < .05). The selective mGluR8 agonist (S)-3, 4-DCPG inhibited TLESR by 54% at 15 μmol/kg (P < .01). Conclusions: mGluR5 antagonists potently inhibit TLESR and reflux in ferrets, implicating mGluR5 in the mechanism of TLESR. mGluR5 antagonists are therefore promising as therapy for patients with GERD. .COPYRGT. 2005 by the American Gastroenterological Association.
TI Inhibition of transient lower esophageal sphincter relaxation and gastroesophageal reflux by metabotropic glutamate receptor ligands
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in the mechanism of TLESR. mGluR5 antagonists are therefore promising as therapy for patients with GERD. .COPYRGT. 2005 by the American Gastroenterological Association.

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AN 2007-0150407 PASCAL
CP Copyright .COPYRGT. 2007 INIST-CNRS. All rights reserved.
TIEN Peripheral versus central modulation of gastric vagal pathways by metabotropic glutamate receptor 5
AU YOUNG Richard L.; PAGE Amanda J.; O'DONNELL Tracey A.; COOPER Nicole J.; BLACKSHAW L. Ashley
CS Nerve Gut Research Laboratory, Hanson Institute, Royal Adelaide Hospital, Australia; Discipline of Medicine, Faculty of Health Sciences, University of Adelaide, Adelaide, Australia; Discipline of Physiology, School of Molecular and Biomedical Sciences, University of Adelaide, Adelaide, Australia
SO American journal of physiology. Gastrointestinal and liver physiology, (2007), 55(2), G501-G511, 48 refs.
ISSN: 0193-1857 CODEN: APGPDF
DT Journal
BL Analytic
CY United States
LA English
AV INIST-670C2, 354000143318710070
CP Copyright .COPYRGT. 2007 INIST-CNRS. All rights reserved.
AB Metabotropic glutamate receptors (mGluR) are classified into group I, II, and III mGluR. Group I (mGluRl, mGluR5) are excitatory, whereas group II and III are inhibitory. mGluR5 antagonism potently reduces triggering of transient lower esophageal sphincter
relaxations and gastroesophageal reflux.
Transient lower esophageal sphincter
relaxations are mediated via a vagal pathway and initiated by distension of the proximal stomach. Here, we determined the site of action of mGluR5 in gastric vagal pathways by investigating peripheral responses of ferret gastroesophageal vagal afferents to graded mechanical stimuli in vitro and central responses of nucleus tractus solitarius (NTS) neurons with gastric input in vivo in the presence or absence of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP). mGluR5 were also identified immunohistochemically in the nodose ganglia and NTS after extrinsic vagal inputs had been traced from the proximal stomach. Gastroesophageal vagal afferents were classified as mucosal, tension, or tension-mucosal (TM) receptors. MPEP (1-10 μM) inhibited
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AN 2005-0396163 PASCAL
CP Copyright .COPYRGT. 2005 INIST-CNRS. All rights reserved.
TIEN Transient lower esophageal sphincter relaxations in dogs are inhibited by a metabotropic glutamate receptor 5 antagonist
AU JENSEN Joergen; LEHMANN Anders; UVEBRANT Anna; CARLSSON Anita; JEMDAL Gunilla; NILSSON Karolina; FRISBY Claudine; BLACKSHAW L. Ashley; MATTSSON Jan P.
CS AstrZeneca R&D Moelndal, 431 83 Moelndal, Sweden; Nerve-Gut Research Laboratory, Royal Adelaide Hospital, Adelaide, South Australia 5000, Australia; Discipline of Physiology, University of Adelaide, Adelaide, South Australia 5000, Australia; Department of Medicine, University of Adelaide, Adelaide, South Australia 5000, Australia
SO European journal of pharmacology, (2005), 519(1-2), 154-157, 21 refs. ISSN: 0014-2999 CODEN: EJPHAZ
DT Journal; Short communication
BL Analytic
CY Netherlands
LA English
AV INIST-13322, 354000138628920220
CP Copyright .COPYRGT. 2005 INIST-CNRS. All rights reserved.
AB Transient lower esophageal sphincter relaxation is the major mechanism for gastroesophageal reflux. The present study was initiated to investigate the potential effect of the metabotropic glutamate 5 (mGlu5) receptor antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), on transient lower esophageal sphincter relaxations in the conscious dog. MPEP (1.4-8.7 μmol/kg i.v.) produced a dose-dependent inhibition of transient lower esophageal sphincter relaxations (59±11% inhibition at 8.7 μmol/kg). In addition, there was a reduction of the number of reflux episodes and an increase in latency time to the occurrence of the first transient lower esophageal sphincter relaxation. No effect was seen on basal lower esophageal sphincter pressure or on swallowing. It is concluded that the mGlu5 receptor antagonist MPEP potently inhibits transient lower esophageal sphincter relaxations and that the mGlu5 receptor is a potential target for treatment of gastroesophageal reflux disease.
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CT Esophageal sphincter; Animal; Dog; mglu5 glutamate receptor; Antagonist; Glutamate; Pyridine derivatives; Gastroesophageal reflux

L10 ANSWER 12 OF 17 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

AN 2007:218238 SCISEARCH

GA The Genuine Article (R) Number: 134NT

TI Peripheral versus central modulation of gastric vagal pathways by metabotropic glutamate receptor 5

AU Young, Richard L. (Reprint); Page, Amanda J.; O'Donnell, Tracey A.; Cooper, Nicole J.; Blackshaw, L. Ashley

CS Level 1 Hanson Inst, Nerve Gut Res Lab, Frome Rd, Adelaide, SA 5000, Australia (Reprint); Royal Adelaide Hosp, Hanson Inst, Nerve Gut Res Lab, Adelaide, SA 5000, Australia; Univ Adelaide, Discipline Med, Fac Hlth Sci, Adelaide, SA, Australia; Univ Adelaide, Sch Mol & Biomed Sci, Discipline Physiol, Adelaide, SA, Australia
richard.young@adelaide.edu.au

CYA Australia

SO AMERICAN JOURNAL OF PHYSIOLOGY-GASTROINTESTINAL AND LIVER PHYSIOLOGY, (FEB 2007) Vol. 292, No. 2, pp. G501-G511.
ISSN: 0193-1857.

PB AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.

DT Article; Journal

LA English

REC Reference Count: 48

ED Entered STN: 8 Mar 2007
Last Updated on STN: 8 Mar 2007
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Metabotropic glutamate receptors (mGluR) are classified into group I, II, and III mGluR. Group I (mGluR1, mGluR5) are excitatory, whereas group II and III are inhibitory. mGluR5 antagonism potently reduces triggering of transient lower esophageal sphincter relaxations and gastroesophageal reflux. Transient lower esophageal sphincter relaxations are mediated via a vagal pathway and initiated by distension of the proximal stomach. Here, we determined the site of action of mGluR5 in gastric vagal pathways by investigating peripheral responses of ferret gastroesophageal vagal afferents to graded mechanical stimuli in vitro and central responses of nucleus tractus solitarius (NTS) neurons with gastric input in vivo in the presence or absence of the mGluR5 antagonist 2-methyl-6-(phenylethynyl) pyridine (MPEP). mGluR5 were also identified immunohistochemically in the nodose ganglia and NTS after extrinsic vagal inputs had been traced from the proximal stomach. Gastroesophageal vagal afferents were classified as mucosal, tension, or tension-mucosal (TM) receptors. MPEP (1-10 mu M) inhibited responses to circumferential tension of tension and TM receptors. Responses to mucosal stroking of mucosal and TM receptors were unaffected. MPEP (0.001-10 nmol icv) had no major effect on the majority of NTS neurons excited by gastric distension or on NTS neurons inhibited by distension. mGluR5 labeling was abundant in gastric vagal afferent neurons and sparse in fibers within NTS vagal subnuclei. We conclude that mGluR5 play a prominent role at gastroesophageal vagal afferent endings but a minor role in central gastric vagal pathways.

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STP KeyWords Plus (R): METABOTROPIC GLUTAMATE RECEPTORS; LOWER ESOPHAGEAL SPHINCTER; GASTROESOPHAGEAL-REFLUX DISEASE; INTRAGANGLIONIC LAMINAR ENDINGS; GABA(B) AGONIST BACLOFEN; SOLITARY TRACT; RAT ESOPHAGUS; INHIBIT MECHANOSENSITIVITY; EXCITATORY TRANSMISSION; SYNAPTIC TRANSMISSION

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AN 2005:950128 SCISEARCH

GA The Genuine Article (R) Number: 963PO

TI Inhibition of transient lower esophageal sphincter relaxation and gastroesophageal reflux by metabotropic glutamate receptor ligands

AU Frisby C L; Mattsson J P; Jensen A M; Lehmann A; Dent J; Blackshaw L A (Reprint)

CS Hanson Inst, Nerve Gut Res Lab, Frome Rd, Adelaide, SA 5000, Australia (Reprint); Hanson Inst, Nerve Gut Res Lab, Adelaide, SA 5000, Australia; Royal Adelaide Hosp, Nerve Gut Res Lab, Adelaide, SA 5000, Australia; AstraZeneca, Dept Res & Dev, Molndal, Sweden; Univ Adelaide, Dept Med, Adelaide, SA 5001, Australia; Univ Adelaide, Discipline Physiol, Adelaide, SA 5001, Australia
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CYA Australia; Sweden

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ISSN: 0016-5085.

PB W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.

DT Article; Journal

LA English

REC Reference Count: 45

ED Entered STN: 29 Sep 2005
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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background & Aims: Transient lower esophageal sphincter relaxation (TLESR) is the major mechanism of gastroesophageal acid reflux. TLESR is mediated via vagal pathways, which may be modulated by metabotropic glutamate receptors (mGluRs). Group I mGluRs (mGluR1 and 5) have excitatory effects on neurons, whereas group II (mGluR2 and 3) and group III (mGluR4, 6, 7, and 8) are inhibitory. This study determined the effect of mGluRs on triggering of TLESR and reflux in an established conscious ferret model. Methods: Esophageal manometric/pH studies were performed in ferrets with chronic esophagostomies. TLESR were induced by a gastric load of 25 mL glucose (pH 3.5) and 30 mL air. Results: In control treated animals,

gastric load induced 3.52 +/- 0.46 TLESRs per 47-minute study, 89.7% of which were associated with reflux episodes (n = 16). The mGluR5 antagonist MPEP inhibited TLESR dose dependently, with maximal 71% +/- 7% inhibition at 35 mu mol/kg (n = 9; P < .0001). MPEP also significantly reduced reflux episodes (P < .001) and increased basal lower esophageal sphincter pressure (P < .05). MPEP inhibited swallowing dose dependently, suggesting a common action on trigger mechanisms for swallowing and TLESR. The more selective analogue, MTEP, had more potent effects (90% +/- 6% inhibition TLESR at 40 mu mol/kg; in = 8; P < .0001). In contrast, the group I agonist DHPG tended to increase TLESR. The group II agonist (2R, 4R)-APDC was ineffective, whereas the group III agonist L-(AP4 slightly reduced TLESR (33% at 11 mu mol/kg; P < .05). The selective mGluR8 agonist (S)-3, 4-DCPG inhibited TLESR by 54% at:15 mu mol/kg (P < .01). Conclusions: mGluR5 antagonists potently inhibit TLESR and reflux in ferrets, implicating mGluR5 in the mechanism of TLESR. mGIuR5 antagonists are therefore promising as therapy for patients with GERD.

TI Inhibition of transient lower esophageal sphincter relaxation and gastroesophageal reflux by metabotropic glutamate receptor ligands

AB Background & Aims: Transient lower esophageal sphincter relaxation (TLESR) is the major mechanism of gastroesophageal acid reflux. TLESR is mediated via vagal pathways, which may be modulated. . . +/- 0.46 TLESRs per 47-minute study, 89.7% of which were associated with reflux episodes (n = 16). The mGluR5 antagonist MPEP inhibited TLESR dose dependently, with maximal 71% +/- 7% inhibition at 35 mu mol/kg (n = 9; P < .0001). MPEP also significantly reduced reflux episodes (P < .001) and increased basal lower esophageal sphincter pressure (P < .05). MPEP inhibited swallowing dose dependently, suggesting a common action on trigger mechanisms for swallowing and TLESR. The more selective analogue, MTEP,. . . reflux in ferrets, implicating mGluR5 in the mechanism of TLESR. mGIuR5 antagonists are therefore promising as therapy for patients with GERD.

STP KeyWords Plus (R): GABA(B) AGONIST BACLOFEN; BRAIN-GUT AXIS; 2-METHYL-6-(PHENYLETHYNYL)-PYRIDINE MPEP; LES RELAXATIONS; ANTAGONIST MPEP; MGLU5 RECEPTOR; IN-VITRO; POTENT; DISEASE; MECHANOSENSITIVITY

L10 ANSWER 14 OF 17 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

AN 2005:949484 SCISEARCH

GA The Genuine Article (R) Number: 964AD

TI Transient lower esophageal sphincter relaxations in dogs are inhibited by a metabotropic glutamate receptor 5 antagonist

AU Jensen J (Reprint); Lehmann A; Uvebrant A; Carlsson A; Jerndal G; Nilsson K; Frisby C; Blackshaw L A; Mattsson J P

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SO EUROPEAN JOURNAL OF PHARMACOLOGY, (5 SEP 2005) Vol. 519, No. 1-2, pp. 154-157.
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PB ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.

DT Article; Journal

LA English

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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Transient lower esophageal sphincter relaxation is the major mechanism for gastroesophageal reflux. The present study was initiated to investigate the potential effect of the metabotropic glutamate 5 (mGlu5) receptor antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), on transient lower esophageal sphincter relaxations in the conscious dog. MPEP (1.4-8.7 mu mol/kg i.v.) produced a dose-dependent inhibition of transient lower esophageal sphincter relaxations (59 +/- 11 % inhibition at 8.7 mu mol/kg). In addition, there was a reduction of the number of reflux. episodes and an increase in latency time to the occurrence of the first transient lower esophageal sphincter relaxation. No effect was seen on basal lower esophageal sphincter pressure or on swallowing.

It is concluded that the mGlu5 receptor antagonist MPEP potently inhibits transient lower esophageal sphincter relaxations and that the mGlu5 receptor is a potential target for treatment of gastroesophageal reflux disease. (c) 2005 Elsevier B.V. All rights reserved.

TI Transient lower esophageal sphincter relaxations in dogs are inhibited by a metabotropic glutamate receptor 5 antagonist

AB Transient lower esophageal sphincter relaxation is the major mechanism for gastroesophageal reflux. The present study was initiated to investigate the potential effect of the metabotropic glutamate 5 (mGlu5) receptor antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), on transient lower esophageal sphincter relaxations in the conscious dog. MPEP (1.4-8.7 mu mol/kg i.v.) produced a dose-dependent inhibition of transient lower esophageal sphincter relaxations (59 +/- 11 % inhibition at 8.7 mu mol/kg). In addition, there was a reduction of the number of reflux. episodes and an increase in latency time to the occurrence of the first transient lower esophageal sphincter relaxation. No effect was seen on basal lower esophageal sphincter pressure or on swallowing.

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ST Author Keywords: glutamate; lower esophageal sphincter; 2-methyl-6-(phenylethynyl)-pyridine; MPEP; gastroesophageal reflux

L10 ANSWER 15 OF 17 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

AN 2005:902107 SCISEARCH

GA The Genuine Article (R) Number: 960JX

TI Recent advances in non-competitive mGlu5 receptor antagonists and their potential therapeutic applications

AU Slassi A (Reprint); Isaac M; Edwards L; Minidis A; Wensbo D; Mattsson J; Nilsson K; Raboisson P; McLeod D; Stormann T M; Hammerland L G; Johnson E

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CYA Canada; Sweden; USA

SO CURRENT TOPICS IN MEDICINAL CHEMISTRY, (2005) Vol. 5, No. 9, pp. 897-911. ISSN: 1568-0266.

PB BENTHAM SCIENCE PUBL LTD, EXECUTIVE STE Y26, PO BOX 7917, SAIF ZONE, 1200 BR SHARJAH, U ARAB EMIRATES.
DT General Review; Journal
LA English
REC Reference Count: 117
ED Entered STN: 15 Sep 2005
Last Updated on STN: 15 Sep 2005
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Extensive research into the functions of glutamate and glutamate receptors in the central nervous system (CNS) has shown an essential role of metabotropic glutamate (mGlu) receptors in normal brain functions, but also in neurological and psychiatric disorders. The precise functions of these receptors remain undefined, and progress toward understanding their functions has been hampered by the lack of selective ligands with appropriate pharmacokinetic properties. The Group I mGlu receptor, mGlu5, is well positioned to regulate and fine-tune neuronal excitability and synaptic transmission through its modulation of various signal transduction pathways and interactions with other transmitter systems. Therefore, the mGlu5 receptor may be an important therapeutic target for the treatment of disorders of the central nervous system. The discovery of MPEP 3, a non-competitive mGlu5 receptor antagonist, provided a potent, selective, systemically active tool compound for proof of concept studies in animal models of various disease states. These studies have led to greater understanding of possible therapeutic applications of mGlu5 receptor antagonists in recent years, suggesting their use in a number of disease states, including chronic pain, various psychiatric and neurological disorders, substance abuse and withdrawal, obesity and gastroesophageal reflux disease (GERD).
Together, these findings have intensified efforts to find other non-competitive mGlu5 receptor antagonists and have led to the discovery of several second-generation compounds, a few of which are in preclinical evaluations. There have been several recent reviews on mGlu receptor. This article highlights recent efforts on the design, synthesis and development of novel, non-competitive mGlu5 receptor antagonists and studies to understand their in vitro mechanisms of action and in vivo pharmacological profiles. Emphasis is also given to recent advances in the potential therapeutic applications of noncompetitive mGlu5 receptor antagonists.

AB . . . receptor may be an important therapeutic target for the treatment of disorders of the central nervous system. The discovery of MPEP 3, a non-competitive mGlu5 receptor antagonist, provided a potent, selective, systemically active tool compound for proof of concept studies in. . . in a number of disease states, including chronic pain, various psychiatric and neurological disorders, substance abuse and withdrawal, obesity and gastroesophageal reflux disease (GERD). Together, these findings have intensified efforts to find other non-competitive mGlu5 receptor antagonists and have led to the discovery of. . .

STP KeyWords Plus (R): METABOTROPIC GLUTAMATE-RECEPTOR; FRAGILE-X-SYNDROME; LONG-TERM POTENTIATION; EXCITATORY AMINO-ACIDS; RAT SPINAL-CORD; BASAL-GANGLIA; PARKINSONS-DISEASE; 2-METHYL-6-(PHENYLETHYNYL)-PYRIDINE MPEP; ANXIOLYTIC ACTIVITY; NEUROPATHIC PAIN

L10 ANSWER 16 OF 17 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2004:738441 SCISEARCH
GA The Genuine Article (R) Number: 813EK
TI The metabotropic glutamate receptor 5 antagonist MPEP inhibits transient lower esophageal sphincter relaxations in the dog
AU Jensen J (Reprint); Lehmann A; Hulander M; Uvebrant A; Carlsson A; Umaerus M; Nilsson K; Frisby C; Blackshaw L A; Mattsson J
SO GASTROENTEROLOGY, (APR 2004) Vol. 126, No. 4, Supp. [2], pp. A632-A632. ISSN: 0016-5085.

PB W B SAUNDERS CO-ELSEVIER INC, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
DT Conference; Journal
LA English
REC Reference Count: 0
ED Entered STN: 10 Sep 2004
Last Updated on STN: 11 Jan 2006
TI The metabotropic glutamate receptor 5 antagonist MPEP inhibits transient lower esophageal sphincter relaxations in the dog

L10 ANSWER 17 OF 17 USPATFULL on STN
AN 2006:152319 USPATFULL
TI Use of mglur5 antagonists for the treatment of gerd
IN Lehmann, Anders, Borghamnsg. 14, Vastra Frolunda, SWEDEN S-421 66
Mattson, Jan, Kullavik, SWEDEN
Stormann, Thomas M., Salt Lake City, UT, UNITED STATES
PA AstraZeneca AB (non-U.S. corporation)
NPS Pharmaceuticals, Inc. (non-U.S. corporation)
PI US 2006128760 A1 20060615
AI US 2003-517869 A1 20030619 (10)
WO 2003-US16223 20030619
20051012 PCT 371 date
PRAI SE 2002-1943 20020620
DT Utility
FS APPLICATION
LREP BIRCH, STEWART, KOLASCH & BIRCH, LLP, P.O. BOX 747, 8110 GATEHOUSE ROAD, SUITE 500 EAST, FALLS CHURCH, VA, 22040-0747, US
CLMN Number of Claims: 15
ECL Exemplary Claim: 1-14
DRWN No Drawings
LN.CNT 396
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the use of metabotropic glutamate receptor 5 antagonists for the inhibition of transient lower esophageal sphincter relaxations. A further aspects of the invention is directed to the use of metabotropic glutamate receptor 5 antagonists for the treatment of gastro, esophageal reflux disease, as well as for the treatment of regurgitation and asthma.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Use of mglur5 antagonists for the treatment of gerd
AB The present invention relates to the use of metabotropic glutamate receptor 5 antagonists for the inhibition of transient lower esophageal sphincter relaxations. A further aspects of the invention is directed to the use of metabotropic glutamate receptor 5 antagonists for the treatment of gastro, esophageal reflux disease, as well as for the treatment of regurgitation and asthma.
SUMM The present invention relates to the use of metabotropic glutamate receptor 5 (mGluR5) antagonists for the inhibition of transient lower esophageal sphincter relaxations. A further aspect of the invention is directed to the use of metabotropic glutamate receptor 5 antagonists for the treatment of gastro-esophageal reflux disease, as well as for the treatment of regurgitation.
SUMM The lower esophageal sphincter (LES) is prone to relaxing intermittently. As a consequence, fluid from the stomach can pass into the esophagus since the. . .
SUMM Gastro-esophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease. Current pharmacotherapy aims at reducing gastric acid secretion, or at neutralizing acid in the esophagus. The major mechanism behind reflux has been considered to depend on a hypotonic lower esophageal

sphincter. However, e.g. Holloway & Dent (1990) Gastroenterol. Clin. N. Amer. 19, pp. 517-535, has shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESRs), i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal in patients with GERD.

SUMM The object of the present invention was to find a new way for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), thereby preventing reflux. More particularly the object of the invention was to find a new and improved way of treating gastro-esophageal reflux disease (GERD), as well as a new and improved way for the treatment of regurgitation.

DETD It has now surprisingly been found that metabotropic glutamate receptor 5 (mGluR5) antagonists are useful for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), and thus for the treatment of gastro-esophageal reflux disease (GERD).

DETD . . . to the use of a metabotropic glutamate receptor 5 antagonist for the manufacture of a medicament for the inhibition of transient lower esophageal sphincter relaxations (TLESRs).

DETD . . . of a metabotropic glutamate receptor 5 antagonist for the manufacture of a medicament for the treatment of gastro-esophageal reflux disease (GERD).

DETD Effective prevention of regurgitation would be an important way of preventing, as well as curing lung disease due to aspiration of regurgitated gastric contents,. . . is the use of a metabotropic glutamate receptor 5 antagonist for the manufacture of a medicament for the treatment of regurgitation.

DETD A further aspect of the present invention is a method for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist is administered to a. . .

DETD Still a further aspect of the invention is a method for the treatment of gastro-esophageal reflux disease (GERD), whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist is administered to a subject in. . .

DETD Yet another aspect of the invention is a method for the treatment of regurgitation, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist is administered to a subject in. . .

DETD The wording "TLESR", transient lower esophageal sphincter relaxations, is herein defined in accordance with Mittal, R. K., Holloway, R. H., Penagini, R., Blackshaw, L. A., Dent, J., 1995; Transient lower esophageal sphincter relaxation. Gastroenterology 109, pp. 601-610.

DETD The wording "GERD", gastro-esophageal reflux disease, is defined in accordance with van Heerwarden, M. A., Smout A. J. P. M., 2000; Diagnosis of. . .

DETD . . . free supply of water, a multilumen sleeve/sidehole assembly (Dentsleeve, Adelaide, South Australia) is introduced through the esophagostomy to measure gastric, lower esophageal sphincter (LES) and esophageal pressures. The assembly is perfused with water using a low-compliance manometric perfusion pump (Dentsleeve, Adelaide, South Australia).. . .

DETD TLESRs is defined as a decrease in lower esophageal sphincter pressure (with reference to intragastric pressure) at a rate of >1 mmHg/s. The relaxation should not be preceded by a. . .

DETD . . . support that metabotropic glutamate receptor 5 antagonists are useful for the inhibition of TLESRs, and thus for the treatment of

GERD.

CLM What is claimed is:

15. A method for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable. . .

16. A method for the treatment of gastro-esophageal reflux disease (GERD), whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or. . .

18. A method for the treatment of, or prevention of, regurgitation, whereby a pharmaceutically and pharmacologically effective amount of a metabotropic glutamate receptor 5 antagonist, or a pharmaceutically acceptable salt or. . .

IT 96206-92-7, 2-Methyl-6-(phenylethynyl)pyridine 219911-35-0
327056-26-8 453567-01-6
(metabotropic glutamate receptor 5 antagonists for treatment of gastroesophageal reflux disease and other conditions)

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